REMARKS

A. Preliminary Remarks

Claims 2-4 and 15-33 are canceled, without prejudice.

Claim 1 is amended and new claims 34-50 are added. Support for the amendments to the claims can be found throughout the specification. For example, support for the amendments can be found at least at page 6, page 8, page 26, pages 32-39, page 44, page 66, Example 4, Example 9, and original claim 4. Thus, the amendments to the claims do not include new matter.

B. Outstanding Rejections

Claims 1 and 4-14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4-14 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled throughout the full scope of the claims.

Claims 1 and 4-14 stand rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) as allegedly anticipated by or, in the alternative, obvious over Coffin *et al.*, Gene Ther. 3:560-566 (1996) (hereinafter, "Coffin *et al.*").

Claims 1 and 4-14 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Coffin *et al.* in view of Pyles *et al.*, WO 98/42195 (hereinafter, "Pyles *et al.*").

C. Patentability Arguments

1. The Rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claim 1 stands rejected as being incomplete for allegedly omitting essential steps. The official action put forth several steps that it deems "omitted" which include "the region where the heterologous gene is/are inserted, what is being treated, what gene is being deleted, what is being measured, or how the expression is determined." Because none of these steps are essential to the method of Claim 1, the applicants respectfully traverse and request reconsideration of the claim.

As amended herein, Claim 1 is directed to a method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo* comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex virus vector

lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. The specification demonstrates that recombinant replicating herpes simplex virus vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid provide prolonged expression of the heterologous nucleic acid in vascular cells when administered *in vivo* to a blood vessel in a mammal.

It is not essential that the person administering the virus actually construct the virus. For example, the virus may be purchased or obtained from another party. Thus, inserting the heterologous gene or deleting a gene is not essential to the claimed method of expressing the heterologous gene. Furthermore, because expression of the heterologous nucleic acid exists whether one measures the expression or not, measuring expression is not an essential step. Moreover, it is not necessary that a disease or disorder be treated using the method of Claim 1. Therefore, because none of the steps put forth in the official action are essential to the invention of Claim 1, the applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph.

Claims 9-11 stand rejected as allegedly vague and indefinite for reciting "polypeptide" or "antisense." The official action contends that the terms "polypeptide" or "antisense" are not defined. According to MPEP § 2173, the primary purpose of the definiteness requirement of claim language is "to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." Breadth is not indefiniteness. MPEP § 2173.04 The terms "polypeptide" and "antisense" are well known in the art and the specification is replete with descriptions and examples of each, *e.g.*, page 5, lines 20-32; page 10, lines 5-15; page 12, lines 17-24; page 13, lines 14-31; page 25, line 21, to page 32, line 10. These descriptions and examples, moreover, are entirely consistent with the ordinary meaning of the terms. Thus, the terms are sufficiently clear that "the public is informed of the boundaries of what constitutes infringement of the patent." The applicants respectfully request withdrawal of the rejection of claims 9-11 under 35 U.S.C. §112, second paragraph. For analogous reasons, the applicants submit that a rejection of any of new claims 34-50 on the same ground would be improper.

2. The Rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 1 and 4-14 stand rejected as allegedly not being enabled throughout the full scope of the claims. The claims are directed to a method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo*, comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. The applicants respectfully submit that, using the specification as a guide, one of ordinary skill in the art can make and use the method of the present claims without undue experimentation.

The specification expressly teaches how to make and use the invention. The examples provide exemplary methods of administration of the HSV viral vectors to a blood vessel. The examples show that the inventive method provides highly efficient infection of vascular cells and expression of the heterologous nucleic acid sequence. Whether the field of gene therapy is highly unpredictable or not is immaterial to whether one of skill in the art, using the present specification as a guide, could administer to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. The specification teaches that the heterologous nucleic acid is expressed.

Of course, the effect of expression of the heterologous nucleic acid on the cell, other cells, or the immune system of the mammal will vary depending on the identity of the heterologous nucleic acid. Nonetheless, the heterologous nucleic acid would still be expressed, and the claimed method is a method of expressing a heterologous nucleic acid. Thus, the method of expressing heterologous *lacZ* (encoding β-gal) teaches the method of expressing a heterologous nucleic acid because the identity of the expressed product does not typically affect the process of expression itself. Therefore, the applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, first paragraph, be withdrawn, and submit that an analogous rejection of any of new claims 34-50 would be improper for the reasons provided herein.

3. The rejection under 35 U.S.C. §102(b) as anticipated by, or in the alternative under §103 as obvious over, Coffin et al. (Gene Therapy, 1996) should be withdrawn

As amended herein, Claim 1 is directed to a method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo* comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. Because Coffin *et al.* does not disclose administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene, Coffin does not anticipate claim 1. Withdrawal of the rejection of claims 1 and 4-14 under 35 U.S.C. § 102(b) is respectfully requested.

Furthermore, in light of Coffin *et al.*, one of skill in the art would not be motivated to administer to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. In fact, Coffin *et al.* teaches away from the invention of claim 1. As described on page 561 of Coffin *et al.*, under "X-gal staining," it is effectively stated that viruses lacking $\gamma_1$34.5 and comprising a heterologous β-gal gene "gave only a relatively low number of blue staining cells" when primary rat cardiomyocytes were infected with such virus, and only a few blue staining cells when primary aortic vascular smooth muscle cells were infected. Moreover, the "Discussion" section (page 565) states "deletion of ICP34.5, while preventing replication in [cardiomyocyte] cells, does not allow efficient gene delivery." Thus, because Coffin *et al.* teaches that HSV viruses lacking $\gamma_1$34.5 display low efficiency in expressing a heterologous nucleic acid in cardiomyocytes and vascular cells contacted *in vitro*, one of skill in the art would not be motivated to administer to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. Withdrawal of the rejection of claims 1 and 4-14 under 35 U.S.C. § 103(a) as being obvious over Coffin *et al.* is respectfully requested. For analogous reasons, the applicants submit that a rejection of any of new claims 34-50 on the same ground would be improper.

4. The rejection 35 U.S.C. §103 as being unpatentable over Pyles et al. (WO 98/42195) and Coffin et al. (WO 98/04726) should be withdrawn

Neither Pyles *et al.* nor Coffin *et al.*, alone or in combination, suggests administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. Because every pending claim comprises this step, all of the pending claims are nonobvious in light of the cited references.

Moreover, the applicants disclosed in the examples the surprising and unexpected results requested by the Examiner. As discussed above, Coffin *et al.* (Gene Therapy, 1996) describes the results of *in vitro* experiments wherein HSV vectors lacking $\gamma_1$34.5 and containing a heterologous gene did not efficiently provide expression of the heterologous gene in contacted primary cardiomyocytes and aortic vascular smooth muscle cells. Further, the articles state that the results indicate that "HSV may be inappropriate for highly efficient gene transfer to the arterial wall." Abstract. Nothing in Pyles *et al.* or Coffin *et al.* (WO 98/04726) contradicts this teaching of Coffin *et al.* (Gene Therapy, 1996). Thus, in light of the cited art, one of skill in the art would not expect efficient expression of a heterologous nucleic acid sequence in a vascular cell *in vivo* upon administering to a blood vessel in a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid.

Example 4 of the specification describes administration of a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid (*lac*Z) to a blood vessel of a mammal (rabbit). Rather than the poor infectivity and expression reported within cells infected *in vitro* (Coffin *et al.*), analysis of the blood vessel revealed surprisingly high infection efficiencies and *lac*Z expression in the adventitia, media, and neointima. Furthermore, the infection rates and stability of heterologous gene expression far exceeded the reported results with other vectors and at a dosage several orders of magnitude less than strategies using adenovirus (page 82, lines 15-25). Thus, in light of the teachings of the cited art, the method of the present claims provides surprising and unexpected results. The applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103(a). For analogous reasons, the applicants submit that a rejection of any of new claims 34-50 on the same ground would be improper.

CONCLUSION

For the forgoing reasons, it is submitted that all of claims 1, 5-14, and 34-50 are in condition for allowance. Should the examiner wish to discuss any further matter, he is invited to contact the undersigned at the number listed below.

Respectfully submitted,

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June 27, 2003 By

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